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Health and Environmental Effects Profile for 1,2,3,4,5-Penta-Bromo-6-Chlorocyclohexane

(U.S.) Environmental Protection Agency
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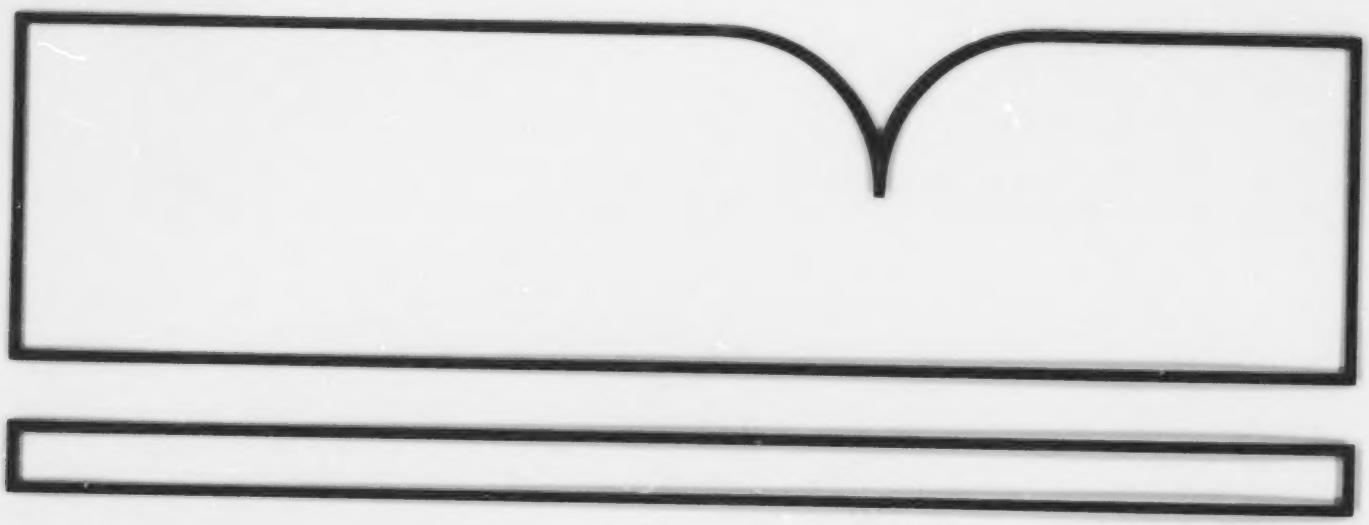

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16. ABSTRACT

The Health and Environmental Effects Profile for 1,2,3,4,5-penta-bromo-6-chloro-cyclohexane was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. 1,2,3,4,5-Penta-bromo-6-chlorocyclohexane has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for 1,2,3,4,5-penta-bromo-6-chlorocyclohexane is 2.3122×10^{-2} $(mg/kg/day)^{-1}$ for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for 1,2,3,4,5-penta-bromo-6-chlorocyclohexane is 1000.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR 1,2,3,4,5-PENTA-BROMO-6-CHLOROCYCLOHEXANE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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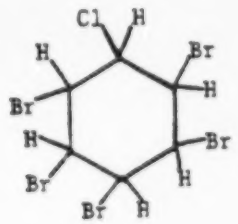
LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
BOD	Biological oxygen demand
CS	Composite score
HPLC	High performance liquid chromatography
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
MED	Minimum effective dose
ppb	Parts per billion
ppm	Parts per million
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SGPT	Serum glutamic pyruvic transaminase
TLV	Threshold limit value
TOC	Total organic carbon
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

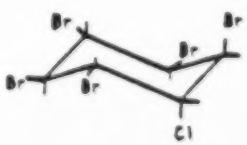
The chemical, 1,2,3,4,5-pentabromo-6-chlorocyclohexane, is also known by the synonyms PBCC and pentabromochlorocyclohexane. The trade name for the product made commercially by Dow Chemical is FR-651. The general chemical structure and the molecular weight and empirical formula for pentabromochlorocyclohexanane are as follows:



Molecular weight: 513.09

Empirical formula: $C_6H_6Br_5Cl$

There are, however, many possible isomers of pentabromochlorocyclohexane, which are designated by the use of Greek letter prefixes (α, β, γ, etc.). Dow indicates the predominant isomer in its product by adding the Latin equivalent (A, B, C, etc.) after the FR-651 designation (e.g., FR-651A) (Gorzsinski et al., 1980a,b). The α-pentabromochlorocyclohexane isomer has the structure shown below (the hydrogen atoms have been omitted for clarity).



The Chemical Abstract Services (CAS) Registry number for 1,2,3,4,5-pentabromo-6-chlorocyclohexane is 87-84-3.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

The properties of pure pentabromochlorocyclohexane and of FR-651 are not identical because Dow's FR-651 contains other compounds. Lickly et al. (1982) found the composition of a ^{14}C-labeled FR-651A sample to be as follows:

α-pentabromochlorocyclohexane	56.4%
α-tetrabromodichlorocyclohexane (CAS No. 30554-72-4)	27.1%
α-tribromotrichlorocyclohexane (CAS No. 30554-73-5)	7.1%
other	9.4%

The physical properties of pentabromochlorocyclohexane and FR-651A are listed in Tables 1-1 and 1-2, respectively.

Chemically, pentabromochlorocyclohexane should react with alkali to form halobenzenes, halocyclohexanes and halocyclohexadienes (U.S. EPA, 1982).

1.3. PRODUCTION DATA

SRI (1984) and USITC (1984) list Dow Chemical in Midland, MI, as the only domestic producer of pentabromochlorocyclohexane. The U.S. International Trade Commission first reported production of pentabromochlorocyclohexane by Dow in 1973 (USITC, 1975).

The Dow patent concerning the manufacture of pentabromochlorocyclohexane describes production as a chlorobromination of benzene with chlorine and bromine in the presence of high energy radiation provided by radioactive cobalt; the products are useful as flame retardants for plastics (Harmer, 1971).

TABLE 1-1

Physical Properties of Pentabromochlorocyclohexane

Property	Description	Reference
Appearance	white solid with almost no odor	Dow, 1982
Melting point	202-203°C	Hutzinger et al., 1976
Boiling point	decomposes at 235°C	Larsen, 1980
Vapor pressure	1.8×10^{-5} mm Hg at 25°C	Dow, 1982
Solubility in water	3.0 ppm ~1 ppm	Anonymous, 1962 Dow, 1982
Log octanol-water partition coefficient	5.8[a]	Dow, 1982
Henry's Law constant	1.2×10^{-5} atm-m^3/mol[b]	
Specific gravity	not available	

[a]It was not clear if the log octanol-water coefficient is a calculated or experimental value (U.S. EPA, 1982).

[b]Calculated from water solubility and vapor pressure data listed above (water solubility of ~1 ppm).

TABLE 1-2

Physical Properties of FR-651A

Property	Description	Reference
Appearance	white to off-white crystalline powder	Dow, 1976
Melting point	180-197°C	Dow, 1982
	190-197°C	Dow, 1976
Boiling point	not available	
Vapor pressure	<0.1 mm Hg at 20°C	McCarty et al., 1978
Solubility in water	<0.1 g/100 g at 25°C	Dow, 1976
	~1 mg/ℓ	McCarty et al., 1978; Goersch and Bailey, 1980
	7.0±0.8 ppm	Bailey and Goersch, 1979; Lewis and Salladay, 1979
	1.20 ppm	Bailey and Goersch, 1979; Lewis and Salladay, 1979
	0.8 ppm	Neumann, 1979
Solubility in non-aqueous solvents	methanol: 3 g/100 g at 25°C	Dow, 1976
	ether: 4 g/100 g at 25°C	Dow, 1976
	acetone: 5 g/100 g at 25°C	McCarty et al., 1978
Log octanol-water partition coefficient	6.0	McCarty et al., 1978
Henry's Law constant	not available	
Specific gravity	not available	

Current production figures for pentabromochlorocyclohexane are not available. The non-confidential portion of the U.S. EPA's TSCA Production File for 1977 lists Dow Chemical as a manufacturer of 1-10 million pounds of pentabromochlorocyclohexane in 1977. There is no reason to believe that current production is not on the same order of magnitude. Import and export data are not available.

1.4. USE DATA

Pentabromochlorocyclohexane is used commercially as a flame retardant in extruded polystyrene foams (Platt and Wallace, 1983; Larsen, 1980). About 1% FR-651A is incorporated into the foam to suppress ignition; the foam is used as an insulating material in the commercial and home construction industry (Lickly et al., 1982; Goersch and Bailey, 1980). Potential use as a flame retardant in rubber has been suggested, but use is limited to polymer systems that are not exposed to excessive processing temperatures. Uses of pentabromochlorocyclohexane other than as a flame retardant were not found.

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

The fate of pentabromochlorocyclohexane in the environment will depend upon its ability to undergo chemical, photochemical and biologically induced alterations, and its transport from one environmental medium to another. The individual processes involved are discussed below for each medium.

2.1. WATER

Hydrolysis studies of pentabromochlorocyclohexane were not found; however, the chemical structure of pentabromochlorocyclohexane suggest that environmental hydrolysis is unlikely to be important. During an aqueous photolysis study of FR-651, Neumann (1979) found no decomposition in the control samples over a period of 4.3 months, which indicates that hydrolysis at pH 7 is very slow.

The aqueous photodecomposition of FR-651 has been studied by Iwamasa and Neumann (1977) and by Neumann (1979). Iwamasa and Neumann (1977) placed 0.1 g of FR-651 in each of three sealed quartz ampules containing 50 mℓ of water, exposed two of them to sunlight for 4 months, and covered the third as a control. The quantity of FR-651 added to the water exceeded the solubility by ~2000 times. At the end of 4 months, all three samples were analyzed for TOC and phenols. Levels of TOC observed in the two photolyzed samples were 9 and 15 mg/ℓ, while TOC was not detected in the control. Each of the photolyzed samples contained six apparent phenols, while no phenols or other UV absorbing species were detected in the control. Table 2-1 lists the phenols and their concentrations found in the photolyzed samples. Neumann (1979) conducted essentially the same experiment by adding 0.1 g of FR-651 to 50 mℓ of water in quartz ampules and exposing them to the sun at ambient outside temperature in Midland, MI, from July to

TABLE 2-1

Tentative Identity and Estimated Concentration of Phenols Found in Photolyzed Samples of FR-651[a]

Tentative Identity	Estimated Concentration[b] (ppb)
Phenol	20
2-Bromo- or 4-chlorophenol	110
4-Bromo- or 2,6-dichlorophenol	120
Unknown chlorobromophenol	80
Unknown chlorobromophenol	140
2,4-Dibromophenol	50

[a]Source: Iwamasa and Neumann (1977)

[b]Concentrations are based upon detector response of nearest eluting chlorophenol standard.

November. Control samples were wrapped in aluminum foil to keep out the light. After the 129th day of exposure, 8.5% of the FR-651 was found to have decomposed in the exposed samples. The main decomposition products found were mono-, di-, tri- and tetra-halobenzenes. Six phenols, which accounted for only 0.07% of the decomposition products, were identified. There was also some isomerization of pentabromochlorocyclohexane to other compounds with the same empirical formula. Unfortunately, due to the limitation in the experimental setup of these two studies (using a quantity of FR-651 which greatly exceeded the solubility), very little can be determined about the rate of pnotolysis of pentabromochlorocyclohexane under environmental conditions. Also, FR-651 contains significant amounts of bromochlorocyclohexanes other than pentabromochlorocyclohexane (see Section 1.2.); therefore, it is necessary to demonstrate that the reaction products do not originate from the impurities present in pentabromochlorocyclohexane. Neumann (1979) has suggested that the photodecomposition of FR-651 may be more rapid than indicated; however, the actual rate of photolysis could not be determined because the quantity of compound tested greatly exceeded the solubility.

The biodegradability of FR-651A was examined in a preliminary study by McCarty et al. (1978) in a standard BOD experiment using seed material from the Dow Michigan Division's Wastewater Treatment secondary effluent. There was no evidence of biodegradation in 20 days as measured by BOD, a finding the authors attributed to the low solubility of FR-651A.

The transport of pentabromochlorocyclohexane in the aquatic environment will depend on the ability of the compound to volatilize, to adsorb to suspended particulate matter and sediment, and to bioaccumulate in aquatic organisms. Specific experimental data for these transport mechanisms were

not found; however, estimates can be made from the physical properties of pentabromochlorocyclohexane listed in Table 1-1. The water solubility (~1 ppm) and the vapor pressure (1.8×10^{-5} mm Hg) of pentabromochlorocyclohexane can be used to calculate the water-to-air ratio (K_w) from the following equation (Swann et al., 1983):

$$K_w = \frac{(0.0624)\ (\text{water solubility in ppm})\ (\text{temp., °K})}{(\text{vapor pressure in mm Hg})(\text{molecular weight in g/mol})} \qquad (2\text{-}1)$$

The calculated K_w value for pentabromochlorocyclohexane is 2013, which means that at equilibrium, ~2000 parts of pentabromochlorocyclohexane will be in the water phase to only 1 part in the air phase. Henry's Law constant can be calculated or estimated by dividing the vapor pressure by the solubility, which results in a value of 1.2×10^{-5} atm-m³/mol. Both of these values (K_w and Henry's Law constant) suggest that pentabromochlorocyclohexane may not significantly vaporize from aquatic media; however, the actual rate of volatilization depends on a number of factors, including the characteristics of the body of water in which the pollutant is found.

The ability of pentabromochlorocyclohexane to be sorbed to organic particulate and sediment matter in the aquatic environment may be predicted from the soil sorption coefficient (K_{oc}). The calculated K_{oc} values listed in Table 2-2 predict that pentobromochlorocyclohexane is likely to be adsorbed tightly onto sediment and suspended particulate matter in water.

McCarty et al. (1978) estimated a BCF of ~2400 for pentabromochlorocyclohexane in trout muscle based on its log octanol-water partition coefficient. The log octanol-water partition coefficient and the water solubility can be used to estimate BCF values from various regression equations developed in the literature. Table 2-3 gives three of these equations and the corresponding calculated BCF. Although these BCF values vary by >1 order of magnitude, they clearly predict that pentabromochlorocyclohexane is likely to bioaccumulate significantly in aquatic organisms.

TABLE 2-2

Soil Sorption Coefficient Estimations for Pentabromochlorocyclohexane

Equation	Calculated Soil Sorption Coefficient (K_{OC})	Reference
Log K_{OC} = 3.64 - 0.55 log WS (in ppm)[a]	4,365	Kenaga and Goring, 1978
Log K_{OC} = 1.377 + 0.544 log K_{OW}[b]	34,000	Kenaga and Goring, 1978
Log K_{OC} = -0.54 log WS (in mole fraction)[a] + 0.44	29,000	Karickhoff et al., 1979
Log K_{OC} = 0.937 log K_{OW}[b]- 0.006	268,000	Brown et al., 1979

[a]WS = water solubility (1 ppm)

[b]Log K_{OW} = log octanol-water partition coefficient (5.8)

TABLE 2-3

BCF Estimations for Pentabromochlorocyclohexane

Equation	Calculated BCF	Reference
Log BCF = 0.76 log K_{ow}-0.23[a]	15,000	Veith et al., 1980
Log BCF = 2.791-0.564 log WS[b]	618	Kenaga and Goring, 1978
Log BCF = 0.935 log K_{ow}-1.495[a]	8,470	Kenaga and Goring, 1978

[a]Log K_{ow} = log octanol-water partition coefficient

[b]WS = water solubility in ppm (1 ppm)

2.2. AIR

Pertinent experimental data regarding the fate of pentabromochlorocyclohexane in the atmosphere were not located in the available literature as cited in the Appendix. Based on the data on PCBs (Cupitt, 1980), physical removal processes, including wet deposition, adsorption on aerosol particulates and dry deposition, are not likely to have any environmental significance. In the absence of experimental data, it is difficult to predict the significance of the chemical removal processes, which include reaction with hydroxyl radicals, ozone or other radicals and photolysis. Aqueous photolysis tests (see Section 2.1.) have shown that pentabromochlorocyclohexane is photolyzed slowly by the sun; however, limitations in the experimental protocol render these results of little relevance to actual environmental conditions.

2.3. SOIL

Lickly et al. (1982) reported the results of aerobic and anaerobic degradation studies in two soils by using ^{14}C-labeled FR-651A. They found that FR-651A consists of three major components (see Section 1.2.; α-pentabromochlorocyclohexane content of 56.4%), but quantified it as a single material. The soils used for the study were Londo sandy loam (pH 6.5 and organic carbon 1.9%) and Commerce loam (pH 7.41 and organic carbon 0.56%). In the aerobic study, the soils were spiked at a ^{14}C-FR-651A concentration of 1.46 ppm (dry soil basis). Table 2-4 shows the results for the Londo sandy loam; results for the Commerce loam were similar. From these results, the aerobic half-life was estimated to be ~10 days. In the anaerobic study, the same soils were spiked with 1.50 ppm ^{14}C-FR-651A after incubation in the absence of oxygen to establish anaerobic conditions.

TABLE 2-4

Aerobic Degradation of ^{14}C-FR-651A in Londo Sandy Loam Soil[a,b,c]

Time (days)	^{14}C-FR-651A[d] in Ethyl Acetate Extract	Degradate(s)[d] in Ethyl Acetate Extract	Total Ethyl Acetate Extract[e]	Acid Extract[e]	Not Extracted[e]	$^{14}CO_2$ Trap[e]	Total[e]
0	1.55	<0.03	1.39	0.01	0.13	NA	1.53
7	0.42	<0.03	0.79	0.08	0.36	0.17	1.40
14	0.21	<0.03	0.43	0.11	0.41	0.31	1.26
28	0.11	0.04	0.34	0.06	0.34	0.49	1.23
56	<0.05	<0.03	0.18	0.10	0.45	0.65	1.38
90	<0.05	<0.03	0.13	0.10	0.46	0.82	1.51

[a]Source: Lickly et al., 1982

[b]Initial ^{14}C-FR-651A equivalent 1.46 ppm

[c]All concentrations in equivalent ppm FR-651A

[d]Determined by HPLC

[e]Quantitated by liquid scintillation counting without chromatography

NA = Not applicable

The results from both soils were similar and predicted an anaerobic half-life for FR-651A of ~5 hours. The degradation products were not identified, and sterile control studies were not performed for comparison; however, the decomposition of the FR-651A was attributable to biological means as evidenced by CO_2 production.

Pertinent data regarding chemical hydrolysis or surface photolysis in soil could not be located in the available literature as cited in the Appendix.

Experimental soil adsorption-leaching data were not found; however, the importance of soil leaching can be predicted by estimating soil sorption coefficients (K_{oc}) from various equations that have been developed through use of water solubility and log octanol-water partition coefficient data. Table 2-2 listed several of these equations and the corresponding calculated K_{oc} values for pentabromochlorocyclohexane. These calculated K_{oc} values predict that pentabromochlorocyclohexane will be bound tightly to soil and, therefore, is not likely to leach significantly in soil. Some leaching has been observed from polystyrene foam (Section 3.1.), but leaching in soil has not been reported.

Pertinent data regarding the volatilization of pentabromochlorocyclohexane from soil surfaces could not be located in the available literature as cited in the Appendix. However, due to the high K_{oc} values and low vapor pressure of pentabromochlorocyclohexane, it is unlikely that volatilization is an important environmental concern.

2.4. SUMMARY

Pentabromochlorocyclohexane entering the aquatic environment may be expected to adsorb significantly to sediment and suspended particulate matter where, based on soil degradation studies by Lickly et al. (1982),

rapid biogradation may occur. Photolysis may play some role, but the degree of importance is not clear. Volatilization will occur at a slow, and perhaps, unimportant rate. Aquatic organisms exposed to pentabromochlorocyclohexane can be expected to strongly bioaccumulate the compound.

In the soil environment, pentabromochlorocyclohexane can be expected to be tightly sorbed (with insignificant leaching) and, based on the Lickly et al. (1982) studies, be quickly biodegraded.

The fate of pentabromochlorocyclohexane entering the atmosphere is unclear due to the lack of experimental data; however, high K_{oc} values for this chemical suggest volatilization from at least one medium would not be expected to occur to a significant extent. Chemical removal through photolysis may occur.

3. EXPOSURE

3.1. WATER

Pertinent data regarding the monitoring of pentabromochlorocyclohexane in water could not be located in the available literature as cited in the Appendix. The U.S. EPA STORET data base has no data for pentabromochlorocyclohexane.

Goersch and Bailey (1980) and Lickly et al. (1982), of Dow Chemical, have suggested that leaching from polystyrene foam insulation (which contains pentabromocnlorocyclohexane) can occur in landfills with water percolating through them. Goersch and Bailey (1980) studied the leaching of FR-651A from ground foam and block foam over a 30-day period using distilled water, and separately with a 0.1 M acetate buffer, both at pH 5 and temperatures of 5, 15 and 50°C. In each case, all three components of FR-651 (pentabromochlorocyclohexane, tetrabromodichlorocyclohexane and trichlorotribromocyclohexane) were found in the aqueous extractant used in the static leaching tests. Equilibrium concentrations of the leachate from both ground and block foam in distilled water were 26, 54 and 70 µg/ℓ at temperatures of 5, 15 and 50°C, respectively. The equilibrium concentrations were reached in <2 days for the ground foam and in 2-4 weeks for the block foam. Similar concentrations were found using the acetate buffer, but equilibrium was reached sooner. These tests suggest that FR-651 foam disposed of in a landfill and contacted with sufficient water can leach pentabromochlorocyclohexane through soil. Pentabromochlorocyclohexane exposed to the soil is, however, likely to be decomposed via microbial degradation (see Section 2.3.), possibly before it reaches groundwater. In cases where the microbial population is depleted, as in the case of a landfill or dumpsite, groundwater contamination is more likely to occur.

3.2. FOOD

Pertinent data regarding food monitoring or exposure could not be located in the available literature. While pentabromochlorocyclohexane can be leached from polystyrene foam, it is not known to be used in food containers.

3.3. INHALATION

Pertinent data regarding air monitoring or inhalation exposure of pentabromochlorocyclohexane could not be located in the available literature as cited in the Appendix.

3.4. DERMAL

Pertinent data regarding the dermal exposure to pentabromochlorocyclohexane could not be located in the available literature as cited in the Appendix.

4. PHARMACOKINETICS

4.1. ABSORPTION

Absorption of pentabromochlorocyclohexane following ingestion, can be inferred from the distribution data (Section 4.2.) of Gorzinski et al., (1980a,b). After 13 weeks of ingestion of a "slurry-dried" mixture of FR-651 by rats, ~1-2% of the compound (measured as total bromine) was detected in the liver, kidney and adipose tissue, indicating absorption by the gastrointestinal tract (Gorzinski et al., 1980a). In another study by Gorzinski et al. (1980b), rats were fed a homogeneous preparation of α-pentabromochlorocyclohexane at a dosage of 600 mg/kg bw/day for 13 weeks; again, highest levels of total bromine were found in the kidneys, followed by liver and adipose tissue, with all three organs showing detectable levels of total bromine of ~2% the ingested dose.

4.2. DISTRIBUTION

Gorzinski et al. (1980a) found that after 13 weeks of ingestion by rats of slurry-dried FR-651 at dosages of 90, 260 or 780 mg/kg bw/day, ~1-2% of the compound (measured as total bromine content) was detected in the kidney, liver and adipose tissue. At the highest dosage level, the bromine content tended to reach a plateau in the kidney (1560±10 µg/g; 200 times control level), liver (773±55 µg/g; 200 times control level) and adipose tissue (278±46 µg/g; 115 times control level). This information was available only in summarized form (U.S. EPA, 1982; TSCA-ITC, 1983).

A second study by Gorzinski et al. (1980b) supported the first experimental evidence of distribution. Rats fed FR-651A at a dose of 600 mg/kg bw/day showed detectable levels of total bromine of ~2% in the kidneys, followed by liver and adipose tissue.

4.3. METABOLISM

Pertinent data regarding the metabolism of pentabromochlorocyclohexane were not located in the available literature as cited in the Appendix. TSCA-ITC (1983) suggested that the metabolism of pentabromochlorocyclohexane may be similar to that of hexachlorocyclohexane, which, according to De Bruin (1976), is dechlorinated and hydroxylated to polyhalophenols or is dechlorinated and complexed with glutathione to yield dichlorophenyl-mercapturic acid.

4.4. EXCRETION

Pertinent data regarding the excretion of pentabromochlorocyclohexane were not located in the available literature as cited in the Appendix.

5. EFFECTS

5.1. CARCINOGENICITY

In an initial TSCA Section 8(e) submission by the Dow Chemical Co. (Blair, 1981), preliminary results of a 2-year feeding study in rats were reported. According to the submission, which has also been reviewed by U.S. EPA (1981; 1982) and TSCA-ITC (1983), increased incidences of polypoid adenomas of the large intestine were observed following dietary administration of either of two different compositions of FR-651 at higher dosages. The two different compositions were described only as "Compound A," containing as its major constituent a single isomer of pentabromochlorocyclohexane, and "Compound B," containing as its major constituent a mixture of isomers.

Blair (1981) reported the preliminary results of the study in which groups of 60 male and 60 female Fischer 344 rats were fed "Compound A" in the diet at concentrations equivalent to dosages of 1, 15 or 50 mg/kg bw/day (males) or 1, 20 or 70 mg/kg bw/day (females) for 2 years. Controls consisted of 96 males and 96 females. An interim kill of 10 rats/sex/group was performed after 1 year.

Histologic examination of unspecified tissues and organs was performed on all animals. Preliminary findings indicated an increased incidence of polypoid adenomas of the large intestine in response to varying doses of "Compound A", as presented in Table 5-1. Proliferative lesions of this type were found at a background incidence of 0-3% in historical controls. The U.S. EPA (1982) concluded that these data indicate that pentabromochlorocyclohexane may be a potential human oncogen. Statistical analysis of the data was not presented by Blair (1981), U.S. EPA (1981, 1982) or TSCA-ITC (1983).

TABLE 5-1

Incidence of Polypoid Adenoma in Fischer 344 Rats Fed "Compound A"[a,b]

Sex	Dose (mg/kg bw/day)	Duration of Treatment	Target Organ	Tumor Incidence (%)
Male	0	2 years	large intestine	1/86 (1%)
	1			1/50 (2%)
	15			0/50 (0%)
	50			5/50 (10%)
Female	0			1/86 (1%)
	1			0/50 (0%)
	20			3/50 (6%)
	70			8/50 (16%)

[a]Source: Adapted from Blair, 1981

[b]Reported to be FR-651A by TSCA-ITC, 1983

Keyes et al. (1982) reported the final results of the study with "Compound B," which was further identified as FR-651C. Although the report stated that the FR-651C sample had been analyzed for composition and isomer content, the results of the analysis were not presented. The test compound was fed to groups of 60 male and 60 female Fischer 344 rats at dietary concentrations equivalent to dosages of 1, 15 or 50 mg/kg bw/day (males) or 1, 20 or 70 mg/kg bw/day (females) for 2 years. There were 96 males and 96 females in the control group. After 1 year, groups of 10 rats/sex/group were sacrificed and necropsied.

Necropsy and comprehensive histologic examination were performed on all rats. Statistical analysis of tumor incidence was performed using the Fischer Exact Test ($p<0.05$, one sided test). At the end of 2 years, cumulative mortality was 20-30% with no differences observed between the treated and control groups. A statistically significant increased incidence of polypoid adenoma of the large intestine was observed in female rats treated at 70 mg/kg bw/day. The incidence of polypoid adenoma in female rats in all groups, as well as that of males for the sake of comparison, are presented in Table 5-2. One of the eight female rats in the 70 mg/kg bw/day group had two adenomas. In addition to these benign tumors, one male at 15 mg/kg bw/day and one female at 70 mg/kg bw/day had a polypoid adenocarcinoma of the large intestine. The incidence of polypoid adenoma or carcinoma is presented in Table 5-2. In a TSCA Section 8(e) supplement to the initial submission (Dow Chemical Co., 1982), the final results of the "Compound A" study were reported to be similar to those of "Compound B". No further information was available.

5.2. MUTAGENICITY

Dow FR-651 was not mutagenic to Salmonella in an Ames assay (Blair, 1981). No other details were given.

TABLE 5-2

Incidences of Polypoid Adenoma and Adenocarcinoma in Fischer 344 Rats Fed FR-651C[a]

Sex	Dose (mg/kg bw/day)	Duration of Treatment	Duration of Study	Vehicle	Target Organ	Incidence of Polypoid Adenomas	Combined Tumor Incidence[b,c]
Male	0	2 years	2 years	diet	large intestine	1/83 (1%)	1/83 (1%)
	1					0/49 (0%)	0/49 (0%)
	15					1/50 (2%)	2/50 (4%)
	50					2/48 (4%)	2/48 (4%)
Female	0					2/85 (2%)	2/85 (2%)
	1					0/50 (0%)	0/50 (0%)
	20					2/50 (4%)	2/50 (4%)
	70					8/50 (16%)[d]	9/50 (18%)[d]

[a]Source: Adapted from Keyes et al., 1982

[b]Incidence as number of tumor bearing rats/number of rats with large intestines examined

[c]Polypoid adenomas and adenosarcomas

[d]$p<0.05$, Fisher Exact Test, one-sided

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of pentabromochlorocyclohexane were not located in the available literature as cited in the Appendix.

5.4. OTHER REPRODUCTIVE EFFECTS

In a subchronic study, Gorzinski et al. (1980b) reported an increase in the testes-to-body weight ratio in male rats fed a diet containing FR-651 (slurry-dried; isomeric composition unspecified) at a concentration equivalent to 780 mg/kg bw/day for 92 days. This increase was considered a secondary result due to decreased body weight in this particular group (Section 5.5.), since the increase was not seen at 90 or 260 mg/kg bw/day. This information was available only in summarized form (U.S. EPA, 1981, 1982).

5.5. CHRONIC TOXICITY

As discussed previously in Section 5.1., 2-year dietary studies, in which "Compound A" (presumably FR-651A) or "Compound B" (defined as FR-651C by Keyes et al., 1982) were administered to rats, have been conducted by Dow Chemical Co. (Gorzinski and Humiston, 1977; Blair, 1981; U.S. EPA, 1981, 1982; TSCA-ITC, 1983; Dow Chemical Co., 1982; Keyes et al., 1982). In these studies, groups of 60 male and 60 female Fischer 344 rats were started on diets containing "Compound A" or "Compound B" at 1, 15 or 50 mg/kg bw/day for males and 1, 20 or 70 mg/kg bw/day for females. Controls consisted of 96 rats/sex/group. After 1 year, 10 rats/sex/group were killed. For "Compound A," the only information available for the interim kill (Gorzinski and Humiston, 1977; Blair, 1981) was that slight dose-related toxicity to the liver and kidney was observed at the higher doses. Other than the reported incidences of polypoid adenoma of the large intestine (see Section 5.1.), neither Gorzinski and Humiston (1977) nor Blair (1981) reported toxic effects after the 2-year kill. A full report of the 2-year study with

"Compound B," including the results of the interim kill, was presented by Keyes et al. (1982); Dow Chemical Co. (1982) indicated that results with "Compound A" were similar.

In the study on "Compound B" (FR-651C), the rats were evaluated for body weight changes, food consumption, palpable masses, mortality, clinical appearance, clinical chemistry parameters, hematologic parameters, urinalyses and organ weights. In addition, gross necropsies were performed on all rats. Comprehensive histologic examination was performed on all control and high dose rats at the 1-year interim kill, and all rats that died after 1 year or were killed after 2 years. Histologic examination of lower dose rats at the 1-year kill was limited to liver, kidneys and gross lesions.

Treatment-related effects in the 1-year rats were as follows. Absolute and relative liver weights were significantly increased in males at 15 and 50 mg/kg bw/day and in females at all dose levels. Increased incidences or severity of gross and histopathologic lesions were limited to the liver and kidneys of high dose males and females. Liver changes were described as multifocal, slight changes in the color of centrilobular hepatocytes and decreased hepatocellular vacuolization in high dose males. Slightly increased severity of chronic progressive glomerulonephropathy in high dose males and females was considered to be a treatment-related acceleration of an age-related process.

Treatment-related effects in the 2-year rats were as follows. Body weight was statistically significantly decreased in high-dose males and females. The decrease in body weight in mid-dose males was not significant, but was considered to be treatment-related. SGPT was significantly decreased in females at 20 and 70 mg/kg bw/day, an effect considered to be treatment-related. Relative liver and kidney weights were increased in high

dose males and females. Significant and treatment-related increased incidences and severity of gross and histopathologic lesions were limited to the stomach, large intestine, liver and kidneys. In the stomach, there was increased thickening of the nonglandular mucosa of high dose males and females and degeneration, increased ulceration and inflammation of the nonglandular mucosa in high dose females. In the large intestine, there was an increased incidence of dilatation, hypercellularity and cellular debris in the crypts of high dose males and mid and high dose females. Increased incidences of polypoid adenoma and a few adenocarcinomas were observed (see Section 5.1.). In the liver, high dose males had increased incidences of multifocal pale or dark foci. High dose females and mid and high dose males had minor hepatocellular cystic degeneration. Mid and high dose males had roughened kidneys, and high dose males and females had increased severity of renal disease. No treatment-related effects were observed at 1 mg/kg bw/day in males or females.

Gorzinski et al. (1980b) fed groups of 10 male and 10 female Fischer 344 rats (6-7 weeks of age) 0 or 600 mg/kg bw/day of FR-651A for 13 weeks. Significant changes in treated rats compared with controls were increases in absolute and relative liver weights, accompanied by a slight enlargement of hepatocytes, and a decrease in staining intensity of the hepatocellular cytoplasm. A decrease in brain-to-body weight ratio was observed in treated males, and decreases in serum alkaline phosphatase activity were observed in treated males at 91 days and treated females at 26 days compared with controls. Serum urea nitrogen and SGPT activity were also decreased in females. Hematologic and urinalysis results were unremarkable.

In a second study by Gorzinski et al. (1980a), groups of 10 male and 10 female Fischer 344 rats (6-7 weeks of age) were fed diets containing equivalent dosages of 0, 90, 260 or 780 mg/kg bw/day of slurry-dried FR-651 for 92 days. Groups of 15 rats/sex were used as a control group. At 780 mg/kg/day, food efficiency and body weight were reduced in both males and females. Gross pathologic findings were unremarkable. Increases in absolute and relative liver weights were observed at 260 and 780 mg/kg/day in males and females. Histologic changes in the liver observed at these dosages were swelling of hepatocytes and alterations in staining and appearance of the cytoplasm. Kidney-to-body weight ratio increased at 780 mg/kg/day for both sexes and in males at 260 mg/kg/day. Brain weight was decreased at 780 mg/kg/day for both sexes and at 90 and 260 mg/kg/day in males. Heart weight decreased in males at 780 mg/kg/day. Serum alkaline phosphatase activity was decreased in all treated groups at 92 days except in females at 90 mg/kg/day. SGPT activity was decreased at 26 days in both sexes at the dose level of 780 mg/kg/day and at 92 days in 90 and 780 mg/kg/day females. Packed cell volume and hemoglobin were increased in the males given 780 mg/kg/day. The results of urinalyses indicated no significant differences between treated groups and controls.

Lockwood and McCollister (1960) fed FR-651 (not otherwise specified) to an unspecified number of Dow Wistar rats at dosages of 0, 10, 30, 100, 300 and 1000 mg/kg bw/day for 90 days in their diet. Liver weight was increased at 300 and 1000 mg/kg/day. Central lobular granular degeneration and necrosis occurred at these same dosage levels, as did an increase in kidney weight with concurrent interstitial and tubular nephritis. No effects were observed at dosages of 30 mg/kg/day for males and 100 mg/kg/day for females; effects in males at 100 mg/kg/day were not reported.

Gorzinski et al. (1979a,b) fed groups of five male and five female Fischer 344 rats FR-651A or FR-651C in the diet at equivalent dosages of 0, 30, 100, 300 or 1000 mg/kg bw/day for 29 days. In the groups fed FR-651A, liver weights were significantly increased for both sexes at the 1000 mg/kg/day dose level; no other effects were observed. In the groups fed FR-651C, there was a decrease in body weight gain for both sexes at the 1000 mg/kg/day level. Significantly increased absolute and relative liver weights were observed in males at 300 and 1000 mg/kg/day. The increase in liver weight in females given 100, 300 or 1000 mg/kg/day was dose-related, but was not statistically significant when compared with controls. Darkened livers were observed in all rats treated at 1000 mg/kg/day.

5.6. OTHER RELEVANT INFORMATION

The oral LD_{50} for pentabromochlorocyclohexane was reported to be >2 g/kg in rats (Vaughn and Keeler, 1975; Keeler and Vaughn, 1976). These investigators also reported minimal eye irritation in rabbits. Limited human exposure in manufacturing situations indicated that moderate eye irritation or some corneal injury may occur. Exposure of dry skin had little effect, but repeated contact on moist skin resulted in erythema, and if the skin was abraded, a superficial burn occurred (Keeler and Vaughn, 1976; Vaughn and Keeler, 1975).

6. AQUATIC TOXICITY

6.1. ACUTE TOXICTY

McCarty et al. (1978) reported that pentabromochlorocyclohexane (FR-651A) at 20 mg/ℓ had no observable adverse effects on fathead minnows, Pimephales promelas, during a static 96-hour bioassay. Following 72-hour exposures, 2.0 mg/ℓ was reported as the maximum safe level of pentabromochlorocyclohexane for the lake emerald shiner, although some mortality occurred at 3.0 mg/ℓ (Anonymous, 1962).

McCarty et al. (1978) conducted static 48-hour toxicity tests of pentabromochlorocyclohexane (FR-651A) on the freshwater crustacean, Daphnia magna. At a level <1.0 mg/ℓ, no adverse effects were observed. The 48-hour LC_{50} determined in this study was 52.7 mg/ℓ, although a partial kill was reported at 1.0 mg/ℓ. The authors pointed out, however, that the levels of FR-651A tested were above the measured water solubility of the product, and that the reported values therefore do not reflect the true toxicity of the chemical (an excess of the recommended amount of acetone was used as a carrier solvent).

6.2. CHRONIC EFFECTS

Pertinent data regarding chronic effects of pentabromochlorocyclohexane were not located in the available literature as cited in the Appendix.

6.3. PLANT EFFECTS

Pertinent data regarding effects of pentabromochlorocyclohexane on plants were not located in the available literature as cited in the Appendix.

6.4. RESIDUE

Based on the log octanol-water partition coefficient of pentabromochlorocyclohexane, McCarty et al. (1978) estimated a BCF of 2400 for trout muscle.

6.5. OTHER RELEVANT INFORMATION

Other relevant information on pentabromochlorocyclohexane was not located in the available literature as cited in the Appendix.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Pertinent guidelines and standards, including EPA ambient water and air quality criteria, drinking water standards, FAO/WHO ADIs, EPA or FDA tolerances for raw agricultural commodities or foods, and ACGIH, NIOSH or OSHA occupational exposure limits were not located in the available literature as cited in the Appendix.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of pentabromochlorocyclohexane were not located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

In Chapter 5, effects in rats of feeding FR-651 (a mixture of hexahalocyclohexanes containing pentabromochlorocyclohexane as the main constituent) were discussed. In some of the studies, the administered compound was a single unspecified isomer of FR-651 (reported to be FR-651A by TSCA-ITC, 1983) and in others, FR-651C. These compounds have been referred to variably as "Compound A" and Compound B," respectively; as alpha isomer and gamma isomer, respectively; and as purified FR-651 (or a single isomer) and a mixture of isomers, respectively, in the various reports and reviews (Blair, 1981; U.S. EPA, 1981, 1982; TSCA-ITC, 1983; Dow Chemical Co., 1982; Keyes et al., 1982). Specific data on the composition and isomeric content of these administered substances were not reported. As discussed in Section 2.1., Lickly et al. (1982) analyzed a sample of ^{14}C-FR-651A and found it to contain 56.4% α-pentabromochlorocyclohexane, along with other hexahalocyclohexanes. Therefore, it is not clear whether any of the studies discussed in Chapter 5 used pure pentabromochlorocyclohexane, regardless of which isomer was designated, and it is impossible to express the dosage levels in terms of pentabromochlorocyclohexane. Both "Compound A" and "Compound B" have been reported to be oncogens.

Dietary administration of "Compound A" (presumed to be FR-651A) or "Compound B" (FR-651C) to rats for 2 years at dosages of 1, 15 or 50 mg/kg bw/day (males) and 1, 20 or 70 mg/kg bw/day (females) resulted in increased incidences of polypoid adenoma and a few adenocarcinomas of the large intestine in the high dose males and females (Blair, 1981; Keyes et al., 1982). The incidences of these tumors were presented in Tables 5-1 and 5-2.

FR-651 was reported to be nonmutagenic in Salmonella typhimurium (Blair, 1981). Information regarding teratogenic and reproductive effects was not located in the available literature as cited in the Appendix.

After an interim kill at 1 year in the 2-year feeding study in rats (Blair, 1981), results of histologic examination revealed liver and kidney damage at dosages of "Compound A" and "Compound B" of 50 mg/kg bw/day for males and 70 mg/kg bw/day for females. In the final report of the study with "Compound B," Keyes et al. (1982) indicated that relative liver weight was increased in males at 15 and 50 mg/kg bw/day and in females at $\geq$1 mg/kg bw/day after 1 year, and described the liver lesions as changes in color of hepatocytes and decreased hepatocellular vacuolization, the kidney lesions were described as increased severity of normal renal disease observed in aging rats.

In the 2-year study, effects of "Compound B" at the high doses (50 mg/kg bw/day for males, 70 mg/kg bw/day for females) included decreased body weight, increased relative liver and kidney weights; increased severity and incidence of thickening of nonglandular mucosa of the stomach in males and females; increased ulceration, inflammation and degeneration of the nonglandular mucosa of the stomach (females); increased incidence of dilatation, hypercellularity and cellular debris in the large intestinal crypts [in addition to the previously discussed increased incidence of polypoid adenomas (males and females)]; hepatocellular cystic degeneration and increased severity of renal disease. At the mid-doses (15 mg/kg bw/day for males, 20 mg/kg bw/day for females), reduced body weight was observed in males, and dilatation, hypercellularity and cellular debris in the large intestine were observed in females. No treatment-related effects were

observed at 1 mg/kg bw/day. The results of the 2-year study with "Compound A" were not available, but Dow Chemical Co. (1982) indicated that effects were similar to those of "Compound B."

Liver and kidney effects were also observed in subchronic studies using FR-651. In a 92-day dietary study (Gorzinski et al., 1980a), rats treated with ≥90 mg/kg bw/day FR-651 had decreased serum alkaline phosphatase and SGPT activities and decreased brain weights. Doses ≥260 mg/kg bw/day were associated with increased liver weight, accompanied by mild histologic changes in the liver.

Lockwood and McCollister (1960) observed increased liver and kidney weight, degeneration and necrosis of the liver and interstitial and tubular nephritis in rats treated with 300 or 1000 mg FR-651/kg bw/day in the diet for 90 days. No-effect levels were reported to be 30 mg/kg bw/day for males and 100 mg/kg bw/day for females (U.S. EPA, 1982; TSCA-ITC, 1983).

In short-term (29 days) feeding studies with rats, Gorzinski et al. (1979a,b) found significantly increased liver weights in both at 1000 mg/kg bw/day, but not at dosages ≤300 mg/kg bw/day when FR-651A was administered. When FR-651C was fed, male liver weight (absolute and relative) was significantly increased at 300 and 1000 mg/kg bw/day, but not at 100 mg/kg bw/day. Increased liver weight was reported to be dose-related in females, but not significantly different from controls.

Although subchronic and chronic studies indicate that FR-651 ingestion at dosages ≥15 mg/kg bw/day results in toxic effects, a dosage of 70 mg/kg bw/day was associated with a statistically significant increased incidence of polypoid adenoma (and of combined polypoid adenoma and adenocarcinoma of the large intestine) in female rats (Blair, 1981; Keyes et al., 1982). The

U.S. EPA (1982) concluded that "pentabromochlorocyclohexane may be a potential human oncogen." It is, therefore, appropriate to derive a carcinogenic potency factor (q_1^*) for humans for pentabromochlorocyclohexane using the data for FR-651, although the composition of the test substances was not clearly indicated. The tumor incidences and data used to calculate the q_1^* for "Compound A" (believed to be FR-651A) are presented in Table 8-1, and for "Compound B (FR-651C) in Tables 8-2 and 8-3. The q_1^* calculation is performed using the computerized multistage linear model, developed by Kenneth Crump and adopted by the U.S. EPA (Federal Register, 1980). The conversion factor used in the calculation of these q_1^* values for humans (assuming 70 kg body weight) from animal data is the cube root of the body weight ratio.

The highest value for the q_1^*, 2.3122×10^{-2} $(mg/kg/day)^{-1}$ was obtained using the incidence data in female rats receiving "Compound A". Assuming the pentabromochlorocyclohexane is the component of FR-651A responsible for the increased tumor incidence, the q_1^* of 2.3122×10^{-2} $(mg/kg/day)^{-1}$ is recommended for estimating the increased lifetime risk of human exposure to pentabromochlorocyclohexane. It should be noted, however, that if it were possible to express the doses in terms of pentabromochlorocyclohexane, the q_1^* would be higher and more protective.

TABLE 8-1

Cancer Data Sheet for Derivation of q_1^*

Compound: "Compound A" (presumed to be FR-651A)

Reference: Blair, 1981

Species, Strain, Sex: rats, Fischer 344, female

Body weight: 0.35 kg (assumed)

Length of exposure (le) = 2 years

Length of experiment (Le) = 2 years

Lifespan of animal (L) = 2 years

Tumor site and type: large intestine, polypoid adenoma

Route, vehicle: oral, diet

Experimental Doses or Exposures* (mg/kg/day)	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested or Examined
0	0	1/86
1	1	0/50
20	20	3/50
70	70	8/50

*Dosages in mg/kg/day were provided in the report.

Unadjusted q_1^* from study = 3.9539×10^{-3} $(mg/kg/day)^{-1}$
Human q_1^* = 2.3122×10^{-2} $(mg/kg/day)^{-1}$

TABLE 8-2

Cancer Data Sheet for Derivation of q_1^*

Compound: "Compound B" (FR-651C)

Reference: Keyes et al., 1982

Species, Strain, Sex: rats, Fischer 344, female

Body weight: 0.35 kg (assumed)

Length of exposure (le) = 2 years

Length of experiment (Le) = 2 years

Lifespan of animal (L) = 2 years

Tumor site and type: large intestine, polypoid adenoma

Route, vehicle: oral, diet

Experimental Doses or Exposures* (mg/kg/day)	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested or Examined
0	0	2/85
1	1	0/50
20	20	2/50
70	70	8/50

*Dosages in mg/kg/day were provided in the report.

Unadjusted q_1^* from study = 3.41355×10^{-3} $(mg/kg/day)^{-1}$
Human q_1^* = 1.9962572×10^{-2} $(mg/kg/day)^{-1}$

TABLE 8-3

Cancer Data Sheet for Derivation of q_1^*

Compound: "Compound B" (FR-651C)

Reference: Keyes et al., 1982

Species, Strain, Sex: rats, Fischer 344, female

Body weight: 0.35 kg (assumed)

Length of exposure (le) = 2 years

Length of experiment (Le) = 2 years

Lifespan of animal (L) = 2 years

Tumor site and type: large intestine, polypoid adenoma or adenocarcinoma

Route, vehicle: oral, diet

Experimental Doses or Exposures* (mg/kg/day)	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested or Examined
0	0	2/85
1	1	0/50
20	20	2/50
70	70	9/50

*Dosages in mg/kg/day were provided in the report.

Unadjusted q_1^* from study = 3.6652×10^{-3} $(mg/kg/day)^{-1}$
Human q_1^* = 2.1434×10^{-2} $(mg/kg/day)^{-1}$

9. REPORTABLE QUANTITIES

9.1 REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

As discussed previously in Chapters 5 and 8, uncertainties regarding the composition and isomeric content of the test substances (FR-651A and FR-651C) administered to rats in subchronic and chronic feeding studies make it impossible to estimate the dosage of pentabromochlorocyclohexane, per se, received by the rats. Although the various reports and reviews of these studies attribute the toxic effects of FR-651 to pentabromochlorocyclohexane, the derivation of the RQ will be performed using the dosages expressed in terms of test substance rather than of pentabromochlorocyclohexane. Therefore, resultant MEDs may be somewhat less conservative than if the dosages were expressed in terms of pentabromochlorocyclohexane.

In the 90-day studies (Gorzinski et al., 1980a,b; Lockwood and McCollister, 1960), toxic effects of FR-651 included increased liver weights, hepatocellular hypertrophy, color changes in hepatocytes, increased incidences of centrilobular degeneration and necrosis, decreases in serum enzymes, increased kidney weights and brain weights and increased incidence and severity of renal disease, and occurred at dosages $\geq$260 mg/kg bw/day (see Chapter 5). Since similar effects were observed in rats after chronic dosing for 1 or 2 years at dosages $\leq$70 mg/kg bw/day (Blair, 1981; Keyes et al., 1982), only the chronic studies will be considered for the derivation of CSs and RQs (Table 9-1). In addition to the toxic effects observed in livers and kidneys, rats treated with FR-651 in the chronic studies had decreased body weights ($\geq$15 mg/kg bw/day), thickening of nonglandular mucosa of stomach (50 and 70 mg/kg bw/day) and ulceration and degeneration (70 mg/kg bw/day) and proliferative and degenerative lesions of the large intestine (50 and 70 mg/kg bw/day) (Keyes et al., 1982). It should be noted that

TABLE 9-1

Composite Scores for Toxicity of Pentabromochlorocyclohexane in Rats Administered FR-651 in the diet[a]

Compound	Animal Dose/ Exposure	Chronic Human MED (mg/day)	RV_d	Effects	RV_e	CS	RQ	Reference
FR-651A[b]	50 mg/kg/day, 1 year	598.5	1.3	Liver and kidney damage, not further described	7	9.1	1000	Blair, 1981; Gorzinski and Humiston, 1977
FR-651C	1 mg/kg/day, 1 year	12.0	3.9	Dose-related, significantly increased relative liver weight at $\geq$1 mg/kg/day	4	15.6	1000	Keyes et al., 1982
FR-651C	15 mg/kg/day, 2 years	179.5	2.1	Reduced body weight, rough appearing kidneys, hepatocellular degeneration	6	12.6	1000	Keyes et al., 1982
FR-651C	20 mg/kg/day, 2 years	239.4	1.9	Increased incidence of dilatation, hypercellularity and cellular debris in large intestine	6	11.4	1000	Keyes et al., 1982
FR-651C	50 mg/kg/day, 2 years	598.5	1.3	Increased incidence and severity of renal disease, hepatocellular degeneration, proliferative and degenerative lesions of large intestine, thickening of nonglandular mucosa of stomach	7	9.1	1000	Keyes et al., 1982

[a]FR-651 is a mixture of hexahalocyclohexanes of which the major constituent is pentabromochlorocyclohexane; the A and C designation refer to different isomers.

[b]The study specified only fr-651 containing a single isomer of pentabromochlorocyclohexane; TSCA-ITC (1983) reported this product to be FR-651A/

statistically significant increased incidences of polypoid adenoma and a single adenocarcinoma of the large intestine were observed in females at 70 mg/kg bw/day (Blair, 1981; Keyes et al., 1982). The increased incidences of histopathologic lesions of the stomach, large intestine and liver were given an RV_e of 6. In cases where increased severity of renal disease was noted, detriment of renal function was inferred, and the effect was given an RV_e of 7. Increased liver weight was given an RV_e of 4. The animal dosages in mg/kg bw/day were converted to human MEDs by multiplying the animal dose by the cube root of the ratio of the rat weight (assumed to be 0.35 kg) to the weight of an average man (assumed to be 70 kg) and multiplying by 70 kg to adjust to mg/day. The MEDs ranged from 12-598.5 mg/day, with corresponding RV_d values ranging from 3.9-1.3. Multiplying the RV_d by the RV_e for a particular dose-effect results in the CS. Each CS obtained corresponded to an RQ of 1000. The highest CS resulted from the data for increased liver weight at 1 mg/kg/day (Table 9-2).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

Preliminary findings from a 2-year feeding study of FR-651 (presumed to be FR-651A) and the final report of 2-year feeding study of FR-651C indicated an increased incidence of polypoid adenomas and a single adenocarcinoma of the large intestine in female Fischer 344 rats (see Section 5.1. and Tables 5-1, 5-2 and 5-3). Since these substances have been tested in only one species and since FR-651 is a mixture of hexahalochlorocyclohexanes, the main component of which is pentabromochlorocyclohexane, there are limited data that pentabromochlorocyclohexane is an animal carcinogen. The U.S. EPA (1982) concluded that the data in rats indicated that pentabromochlorocyclohexane may be a potential human oncogen, although there is no direct evidence of a causal association between exposure and human cancer, and no

TABLE 9-2

Pentabromochlorocyclohexane[a]

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral/diet
Dose[b]:	12.0 mg/day
Effect:	increased liver weight
Reference:	Keyes et al., 1982
RV_d:	3.9
RV_e:	4
Composite Score:	15.6
RQ:	1000

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[a]The administered compound was FR-651C, a mixture of hexahalochlorocyclohexanes of which pentabromochlorocyclohexane is the major component.

[b]Equivalent human dose

epidemiological studies were found in the available literature cited in the Appendix. Therefore, it is appropriate to place pentabromochlorocyclohexane in the IARC Group 3, a suspected carcinogen, which is a chemical or group of chemicals that cannot be classified as to its carcinogenicity for humans.

Although pentabromochlorocyclohexane would be classified as an IARC group 3 chemical, the dose-response data in rats for increased incidences of polypoid adenomas and combined adenomas and adenocarcinomas of the large intestine following dietary exposure to FR-651A and FR-651C have been used to calculate potency factors (F or $1/ED_{10}$) for pentabromochlorocyclohexane (Tables 9-3 and 9-4) using the linearized multistage model developed by Crump and adopted by the U.S. EPA (Federal Register, 1980). The highest resultant value for the unadjusted $1/ED_{10}$ is 2.3×10^{-2} $(mg/kg/day)^{-1}$. The unadjusted $1/ED_{10}$ value was converted to an equivalent value for humans, $F = 1.35 \times 10^{-1}$ $(mg/kg/day)^{-1}$ by multiplying the animal value by the cube root of the ratio of the weight of a rat (assumed to be 0.35 kg) to the average weight of a man (70 kg). Since the length of the experiment was equal to the lifespan of the rat, no correction for lifespan was necessary.

Since the IARC Group is 3 and the $1/ED_{10}$, or F factor is <1, pentabromochlorocyclohexane is placed in Potency Group 4 and, therefore, ranks low in the Hazard Ranking Scheme for Reportable Quantities under CERCLA.

It should be noted that a higher F factor would be obtained had it been possible to express the dosages of FR-651 in terms of pentabromochlorocyclohexane; however, it is doubtful if the higher F factor would have placed pentabromochlorocyclohexane in a higher Potency Group.

TABLE 9-3

Derivation of Potency Factor (F)

Agent: Pentabromochlorocyclohexane (FR-651A)[a]

Reference:	Blair, 1981; Gorzinski and Humiston, 1977			
Exposure route:	oral			
Species:	rat			
Strain:	Fischer 344			
Sex:	female			
Vehicle or physical state:	diet			
Body weight	0.35 kg[b]			
Duration of treatment:	2-years			
Duration of study	2-years			
Lifespan of animal:	2-years			
Target organ:	large intestine			
Tumor type:	polypoid adenoma			
Experimental doses/ exposure (mg/kg/day):	0	1	20	70
Transformed doses[c] (mg/kg/day)	0	1	20	70
Tumor incidence:	1/86	0/50	3/50	8/50
Unadjusted $1/ED_{10}$:	2.3×10^{-2} (mg/kg/day)$^{-1}$			
$1/ED_{10}$ (F Factor):	1.35×10^{-1} (mg/kg/day)$^{-1}$			

[a]Reported in study to be a single isomer of pentabromochlorocyclohexane, but later reported by TSCA-ITC (1983) to be Fr-651A.

[b]Estimated

[c]Reported

TABLE 9-4

Derivation of Potency Factor (F)

Agent: Pentabromochlorocyclohexane (FR-651C)

Reference:	Keyes et al., 1982							
Exposure route:	oral							
Species:	rat							
Strain:	Fischer 344							
Sex:	female							
Vehicle or physical state:	diet							
Body weight	0.35 kg[a]							
Duration of treatment:	2 years							
Duration of study	2 years							
Lifespan of animal:	2 years							
Target organ:	large intestine							
Tumor type:	polypoid adenoma				polypoid adenomas or adenocarcinomas			
Experimental doses/ exposure (mg/kg/day):	0	1	20	70	0	1	20	70
Transformed doses[b] (mg/kg/day)	0	1	20	70	0	1	20	70
Tumor incidence:	2/85	0/50	2/50	8/50	2/85	0/50	2/50	9/50
Unadjusted $1/ED_{10}$:	1.83×10^{-2} (mg/kg/day)$^{-1}$				1.96×10^{-2} (mg/kg/day)$^{-1}$			
$1/ED_{10}$ (F Factor):	1.07×10^{-1} (mg/kg/day)$^{-1}$				1.15×10^{-1} (mg/kg/day)$^{-1}$			

[a]Estimated

[b]Reported

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in November, 1984. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

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